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10/591,087	08/29/2006	Pierre Monsan	BKR-106	6343

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,087	MONSAN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/2/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-33 and 36-38* is/are pending in the application.

4a) Of the above claim(s) *21-24,27-30 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20,25,26,31-33,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 19-33 and 36-38 are pending in the application.

Claims 21-24, 27-30 and 36 are withdrawn from further consideration.

Claims 34-35 are cancelled.

Claims 19-20, 25-26, 31-33 and 37-38 are under examination.

Withdrawn Objection/Rejection

In view of the amendments to the specification cancelling the hyperlink and/or other form of browser-executable code the objection to the specification is withdrawn. Also, the rejection of the claims under 35 USC 112, second paragraph is withdrawn. (Please note that the inadvertent inclusion of the rejection of claim 29 under this statute is regretted. Claim 29 had been withdrawn from consideration as shown in the Status of Claims above).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-20, 25-26, 31-33 and 37-38, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. There is no definition for the variable n in claim 19, which could include an infinite number of populations of cells.

B. Claim 19 is indefinite as to the upper limit of the "more" than one substrate. The metes and bounds of said term is not positively defined in the specification or claims and includes an infinite number of substrates.

C. The claim "said selected host cells having the phenotype (Ai+, B+)" is unclear as to the kind of phenotype made by the referenced (Ai+, B+). This is inconsistent with the preamble which does not recite for the said change in phenotype. It is not clear as to the change in phenotype included or precluded in the (Ai+, B+) cells.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 19-20, 25-26, 31-33 and 37-38, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over

Handelsman et al (USP 7008767) in view of Hoch (USP 6368793) of reasons of record as reiterated below.

Handelsman discloses throughout the patent at e.g., col. 2, line 9 up to col. 4, line 45, including the drawings:

> ..Methods.. for identifying genes from microbial organisms, the gene products of which are involved in biochemical transformation reactions that produce, for example, small organic molecules by de novo synthesis, or that chemically modify molecules ectopically provided in the microbe's environment. In general, the method provides host cells which have been engineered to express the opening reading frames of genomic DNA sub-cloned from a heterologous microorganism. The subject method detects changes in the phenotype of the host cell which are dependent on expression of open reading frames from the genomic DNA, e.g., which may be marked by altered biosynthetic capabilities……
>
> Thus, for example, there is provided a method for identifying a product of a biosynthetic pathway, comprising i) providing host cells containing a replicable vector including genomic DNA isolated from a source of uncultivated microorganisms (metagenomic library, as claimed), which host cells are provided under conditions wherein expression of open reading frame sequence(s) of the genomic DNA occurs; and ii) detecting a compound produced by the host cells, e.g., relative to host cells lacking the genomic DNA. (Reads on claim 19)
>
> …A method for identifying non-proteinaceous compounds produced by a uncultivated microorganisms, comprising i) generating a library of host microorganism(populations of cells, as claimed in claim 19) transfected with a variegated population of vectors containing genomic DNA isolated from a sample of uncultivated microrganisms, which genomic DNA includes open reading frame (ORF) sequences which can be expressed from the vector in the host microorganism; ii) culturing the transfected host microorganism under conditions wherein the ORFs are

expressed; iii) detecting ectopic production of non-proteinaceous compounds by the host microorganisms.

The host microorganism is a species from the

FIG. 1: pBeloBAC11 vector(reads on library of nucleic acid of claim 19).

FIG. 3: is a table illustrating the average size inserts in various BAC libraries described in the art.

FIG. 5: is a table describing the phenotypes confered on the host cell by the expression of the Bacillus cereus BAC library.

Handlesman discloses the variegated population of cells at e.g., col. 9, line 64 up to col. 10,line 3 and col. 21, line 65 up to col. 22, line 59.

Handelsman further discloses at e.g., col. 30,line 49 up to col. 31, line 40:

A High-Throughput Robotic Screening of BAC Clones for Production of Natural Products:

The high throughput processing and analysis of large genomic libraries by the subject method can be automated, e.g., using automated/robotic systems. The automation can include, for instance, such activities as: 1) arraying and storage of BAC libraries; 2) growth and separation of cells/conditioned culture media; and 3) testing conditioned media in biological and biochemical assays. These are outlined below for the exemplary embodiment of a BAC genomic DNA library. The detailed methodologies will vary from one embodiment to the next, but can be readily implemented by those skilled in the art.

Arraying and storage of BAC clones: Following ligation of the DNA into BAC vectors, the ligation mixture is transfected into a suitable host cell, and BAC-containing colonies are selected. If the number of clones recovered is small (e.g., less than 1000), then arraying into glycerol stocks can be accomplished manually. However, if libraries

of more than 10,000 clones are obtained, then arraying is best accomplished using an automated colony picking robot. Growth for expression of natural products and separation of culture: Clones can be inoculated for growth in deep-well 96-well plates, e.g., by using an automated pipetting station. Growth conditions can be established, e.g., using control strains. Following growth, culture media is isolated either by centrifugation and removal of supernatants or by filtration. Residual cells in the isolated culture media can be killed using chloroform vapors.

High throughput assays: The conditioned media can be tested for activity in high throughput biochemical or biological assays adapted for automated readouts. For instance, the method can employ established procedures for robotic antimicrobial testing. In general, such assays are performed in multi-well plates (96 or 384) or by placing small aliquots of conditioned media onto plates seeded with a bacterial or fungal lawn or the like. The goal is to develop an automated method that is sensitive and rapid. In addition to antimicrobial assays, as described above the culture supernatants can be tested in biochemical assays, such as competitive binding assays or enzyme activity assays, as well as whole cell assays, e.g., which detect changes in phenotype dependent on addition of conditioned media. To increase throughput, it may be desirable to test pools of culture supernatants in certain instances.
See the Examples for a detail description of the method.

Handelsman does not disclose that the only source of an element essential to growth is either the substrates or the product produced by the biosynthetic pathway. However,

Hoch discloses throughout the patent at e.g., col.1, line 34 up to col. 3, line 64:

A biocatalytic or metabolic pathway consists of a series of protein catalysts (enzymes) which catalyze the conversion of a starting material to the final product. A general

process to identify the metabolic pathway from a source compound to a target compound involves the creation/identification of an easily genetically-manipulatable organism containing an inducible signal, which is activated when a target compound is metabolized. This is followed by the screening of nucleic acid in this organism to identify genes which metabolize the source compound to the target compound.

An example of a selection strategy which can be used to identify the metabolic pathway from a source compound to a target compound is diagrammed in FIG. 11. As a first step, microbial isolates are selected that are capable of metabolizing a target compound "T", but not a source compound "S", to an essential factor. Essential factors can include elements like carbon…….. In a second step, the pathway responsible for the catabolism of compound "T" is identified and made conditional. That is, the gene(s) for the pathway is cloned and placed under control of an inducible promoter such that growth on the target compound is turned "ON" only when the inducer is present. This engineered strain is referred to as the "tester strain". The third part of the strategy is the transfer of foreign DNA from environmental sources into the tester strain, followed by selection for growth on the source compound "S" in the presence of inducer. Such positive clones either are capable of metabolizing compound "S" in the absence of inducer, in which case utilization of "S" does not require prior conversion to compound "T" (FIG. 11; pathway I), or alternatively metabolize compound "S" only when "T" catabolism is "ON", suggesting that utilization of "S" proceeds via compound "T" to intermediary metabolism (FIG. 11; pathway II). These latter clones are further analyzed and the biocatalysts for the conversion of "S" to "T" are characterized. A specific embodiment of the metabolic selection strategy is shown in FIG. 12, where "S" is 2-keto-L-gulonate (2-KLG), and "T" is ascorbic acid (AsA) which can be metabolized to carbon and energy.

The term "screening" as used herein refers to methods for identifying a nucleic acid sequence of interest. Preferably, the method permits the identification of a nucleic acid sequence of interest among one or more sequences, more preferably among hundreds (100, 200, . . .

900), most preferably among thousands (1,000, 2,000, . . . etc.) or more. The sequences to be screened can be isolated from one or more organisms. Preferably, the sequences are isolated from hundreds of organisms, more preferably from thousands or more organisms. The term "screening" may include both classical screening, whereby expression of the nucleic acid results in a phenotype that can be identified (for example by having a colony with the nucleic acid of interest change color, fluoresce, or luminesce), and may also include classical selection, where typically the phenotype to be identified is growth on selective media. By "selective" is meant media on which the host strain will not grow or grows poorly, but that strains with the nucleic acid of interest will grow in a manner which can be readily distinguished from host strain growth by methods well-known in the art.

Growth in the absence of the inducer indicates that metabolism of the source compound to the essential element or factor does not require prior conversion to the target compound, rather it may proceed directly, or through an intermediate, to the essential element or factor. When conversion directly to the target compound is the desired result, further work is necessary to obtain the desired genes. methods of obtaining the desired genes include: re-selection of DNA from other sources; random mutation of the DNA followed by re-selection; knocking out (deleting or blocking the expression of genes by methods well-known in the art) the genes that allow the direct conversion to the essential element or factor or from an intermediate to the essential element or factor followed by re-selection; etc.

Alternatively, if the intermediate is freely interconvertable with the desired target compound as well as to the essential element, growth in the absence of the inducer may be an acceptable outcome, or even desirable. By "freely interconvertable" is meant that an enzymatic pathway is present to allow the intermediate to be converted to the target. The interconvertability of the compounds would also be determined using the methods described above for obtaining a pathway directly to the target compound.

Samples from diverse natural environments were collected to use for the isolation of microbes that can utilize ascorbic

> acid (AsA) as the sole carbon source. No bacterial species has previously been reported to grow on AsA minimal medium.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to test in the method of Handelsman the substrate or product by the growth of said product or substrate as taught by Hoch. There would be a reasonable expectation of success in measuring the growth of the product since Hoch has extensively discussed the conditions by which the growth can be tested or measured. Thus the test of products or substrates based on its growth is a predictable result as the conventionality of said test is taught by Hoch, supra.

If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007).

Response to Arguments

Applicants state that Handelsman et al. fail to teach testing in parallel said population of transformed host cells on minimum media containing either one or more substrate(s) {Ai},

or said product {B } as the only source of an element essential to growth; and selecting said host cell(s) capable of growth on a minimum medium containing one or more substrate(s) {Ai } and on a mininmm medium containing said product {B } said selected host cell(s) having the phenotype (Ai+ ; B+). Handelsman et al. do not disclose nor suggest that the screening assay is carried out on a medium containing one of the substrates as the only source of an element essential to growth, and on another medium containing the product produced by the biosynthetic pathway, as the only source of an element essential to growth.

In reply, applicants' arguments are not commensurate in scope with claim 19. (Please note that claim 1 has been cancelled.) Claim 9, step c recites parallel testing alternatively the substrates or product in the same medium not one or more substrates in one medium and product in a different medium as argued. Claim 19, step © recites:

> c) testing in parallel said population of transformed host cells on minimum media containing either one or more substrates(Ai), **or** said product {B} as the only source of an element essential to growth.

Furthermore, the preamble recites the transformation of one or more substrates into a desired product. This is inconsistent with the above argument of screening two different media, one for the substrate(s) and one for the

product. This seems to also go against the conventional wisdom in the art of determining the transformed product of the substrates(genes) to determine the transformed product of the substrate or cells that produce said product. Nonetheless, the parallel testing of the substrate and product is taught, or at least suggested, by disclosure of Handelsman of a “biosynthetic pathway". Handelsman defines said pathway as a set of anabolic or catabolic biochemical reactions for converting (transmuting) one chemical species (substrates, as claim) into another (product, as claim). [The biosynthetic (enzymatic) pathway of converting a substrate into a transformed product is a well known process in the art.] For instance, Handelsman discloses the antibiotic biosynthetic pathway which refers to the set of biochemical reactions which convert primary metabolites to antibiotic intermediates and then to antibiotics, (col.6, lines 40-46). The determination of substrate and product is disclosed at e.g., col. 25, lines 30-34. This determination would have been obvious in light of the knowledge in the art that substrates are not completely transformed into product(s). One could therefore assay alternatively the presence of both the substrate and product or the presence of the either the substrate or product. Handelsman

discloses at col. 29, lines 46-49, the detection step of parallel testing to detect a phenotypic change in the host cell which is induced by products of the expression of the heterologous genomic sequences. The growth is done in deep-well 96-well plates (or multi well) (known in the art as parallel testing), e.g., by using an automated pipetting station (col. 31, lines 3-10. See further the high throughput (HT) assay disclose by Handelsman above.

Applicants argue that the method disclosed in Hoch requires the use of a specific genetically modified strain, a "tester strain". In said strain, the catabolism of the product of the metabolic pathway of interest is active only in the presence of an inducer. But recognize that to obtain this "tester strain" in which the catabolism of the product is made conditional, a screening step on a growth medium containing said product as the only source of an essential element is required. However, the screening of host cells after transformation is carried out in the presence of the substrate and in the presence or the absence of the inducer, but always in the absence of the product. This screening method is detailed in example 3 where it is stated (at column 33, lines 5-9): "This library is then

transfected into the tester strain and the resulting pool of transfected cells selected for growth on the source compound (2-KLG in the example) in the absence of the target compound (ascorbate in the example) and the presence of the inducer" (emphasis added). Thus, Hoch fails to describe or to suggest the screening of transformed host cells on both a medium containing the product of the metabolic pathway of interest and a medium containing the substrate of said pathway and cannot remedy the deficiencies of Handelsman et al.

In reply, attention is directed to the disclosure of Hoch above, to reiterate:

> Growth in the absence of the inducer indicates that metabolism of the source compound to the essential element or factor does not require prior conversion to the target compound, rather it may proceed directly, or through an intermediate, to the essential element or factor...
>
> Alternatively, if the intermediate is freely interconvertable with the desired target compound as well as to the essential element, growth in the absence of the inducer may be an acceptable outcome, or even desirable. By "freely interconvertable" is meant that an enzymatic pathway is present to allow the intermediate to be converted to the target. The interconvertability of the compounds would also be determined using the methods described above for obtaining a pathway directly to the target compound.

Thus, for Handelsman to have successfully assayed the transformed cell would have indicated, at least implicitly, the growth of the cell in a medium containing the substrate and product. The transformation of the substrate into the product in the transformed cell would indicate the survival of the substrate or product solely in the medium to result in a transformed cell. This is explicitly taught by Hoch. The combined teachings of HAndleman and Hock would therefore lead one having ordinary skill in the art to the claimed method. There is nothing new and unobvious about the claim method. The biosynthetic (enzymatic) pathway of obtaining a product from a substrate in a transformed host cell under a minimum essential growth media of the substrate/product is no more than the predictable use of prior art elements according to their established functions." KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007).

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS

of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 21-24, 27-30 and 36 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639